CASE VIII.—Mrs. W., aged thirty-six years. Both parents were rheumatic. Her father had heart and kidney disease.

She has been married seventeen years. Seven years ago she was operated upon for the removal of one ovary. The same year she developed asthma which has been present at times ever since. She has always been of a nervous, worrying disposition.

Complains of asthma, mental depression, and fits of crying. She is easily tired. She has worried a great deal about her husband's health. Her bowels are constipated and she is passing only thirty-two ounces of urine in twenty-four hours.

Her symptoms are not attended with much distress, but are gradually becoming more severe. Heart and lungs are normal. No abnormalities of position of viscera noted. Abdomen is pendulous. There is some asymmetry noted. There are no gross stigmata of hysteria.

Examination of urine at the Philadelphia Clinical Laboratory shows indican very high; otherwise normal.

After treatment that was principally dietetic and hydrotherapeutic together with massage and regulated exercises, she became much better. Nine months later examination of her urine showed a normal output of indican.

In the above cases certain points stand out prominently. The first is hereditary taint and a neuropathic susceptibility. The second is the symptom of fear in its various phases—so common in intestinal diseases. The third and most important as far as treatment is concerned, is the constant condition of intestinal putrefaction that has had to be covercome before any relief was achieved; this was in many of the cases associated with insufficient elimination of urine. In cases of this kind there is often a hysterical taint engrafted on the original trouble that must be considered in treatment.

THE INDICAN REACTION AS EVIDENCE OF ENTEROGENIC INTOXICATION.

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IT is conceded that there is great danger in removing any symptom from its clinical surroundings for the purpose of weighing its intrinsic worth; but if there is sufficient evidence to formulate working rules, that danger should not prevent us from seeking to study limitations. The danger is probably no greater with any other clinical test than it is with the Jaffé or Obermeyer reaction in the urine. Indican is present in excess so frequently, not only as evidence of a primary pathological process, but of a complicating condition, that its very frequency leads to misinterpretation.

Further reason for this inquiry is found in the fact that the indican reaction is really the only test available to the general practitioner as an index of enterogenic intoxication.[1] Partition estimations of the sulphuric-ether excretion in twenty-four hours may be exceedingly valuable, but such work is ordinarily out of reach. The same may be said of bacteriological or chemical examination of the feces. Estimations of sulphur intake with the food and its ratio with the sulphur of the urine are usually limited to institutions for medical research. Furthermore, a few observations have been published which make one feel that the simple indican test is a better clinical indication of intoxication arising from putrefactive processes in the intestine than other more refined methods; or at least is a better indicator of the capacity of the organism to assimilate nitrogenous food.

The following evidence is presented in the hope that it will stimulate interest and confidence in the Jaffé and Obermeyer tests. It is drawn largely from laboratory observations, because of the general pessimism which exists among many such workers as to the value of the indican reaction. Precision tests should be devised as soon as possible, but in the meantime walking with a crooked stick is better than stumbling with no stick at all. No attempt will be made to discuss the interpretation of excessive urinary indican. That is a matter of clinical experience. But if some knowledge can be gained of the origin and the difficulties which befall the precursors of indican in the organism, the interpretation will naturally tend toward truth.

The work of Ellinger[2] has removed any doubt which may have existed in the past as to the source of urinary indican. In those starving animals which could be prevented from eating their own feces, the indican reaction in the urine subsided and disappeared as death approached. It could therefore not be formed during the course of proteid metabolism. Gentzen[3] has proved that the injection of skatol-amino-acetic acid (the mother substance of indol) into the cecum was followed by an abundant indican excretion. If ingested with the food, or injected into the rectum, it was metabolized. Increased excretion of indican secondary to putrid empyema or putrefying fœtus *in utero* is of rare occurrence. It is not in this class of cases that the reaction is of assistance in diagnosis, while by no known means can the intestine as a source be excluded. Abscess does not cause it (Beckmann).[4]

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[1] The terminology is unfortunately ambiguous. Intoxications arising from saccharo-butyric fermentations in the intestines are not considered, but only those arising from proteid putrefaction.

[2] Zeit. f. physiol. Chemie, 1903, xxxix, 44. Many animal experiments have been undertaken for the purpose of working out problems connected with the etiology and effects of gastro-intestinal intoxications. It seems as if too much importance as applied to man has been attached to some of them, particularly to those which involve conditions in the intestine. The habits of different animals have marked effects on intestinal putrefactive processes. Dogs are very apt to excrete large quantities of indican. This fact is probably traceable to eating filthy food and their fondness for meats. Allowance should be made for these differences in habit and for the lack of exercise which most experimental animals experience.

[3] Ellinger and Gentzen, Hofmeister's Beiträge, 1903, iv, 171.

The formation of indol is, therefore, limited to the intestine, and it appears during the course of proteid putrefaction and as the result of microbic activity. The conditions which promote its formation are pertinent points for inquiry in considering the excretion of indican in the urine.

Chemical Considerations. On the rough average, the aromatic nucleus of the proteid molecule—of which preformed indol is a part —amounts to about 5 per cent. In some proteids it is absent (gelatin), while in others it may exceed that amount. If it could be assumed that disintegration of the proteid molecule under bacterial influences always took place along fixed lines, and therefore always led to the same end-products, the problem would be much simplified. It would be possible to work out with mathematical accuracy the amount of indol which could be formed from any given proteid.[5] This assumption is not possible. Under some circumstances no indol may be formed, while under different conditions indol may be formed to some extent at the expense of other end-products.

For reasons which will appear later, there are objections in applying these laboratory results too literally to putrefaction in the intestine. In case the end-products of bacterial digestion are not removed, as would obtain in the intestine (even if mixed fecal bacteria are employed and other conditions are imitated), there is a tendency for the activity of the bacteria to be limited as the end-products increase in concentration. Bacterial autolysis is undoubtedly favored; or further activity is expended in dissociation of substances already formed into the simplest end-products.

Indol formation, except in grossly pathological states, is confined to the cecum and the ascending and transverse colons. Not more than 14 per cent. of ingested nitrogen passes the ileocecal valve in approximately healthy conditions (Mayfadyen, Nencki, and Sieber[6]). This includes nitrogen in the form of true excrementitious matter derived from the mucosa above and the secretion of glandular organs contributory thereto. From 6 to 10 per cent. passes the rectum in the feces. It[7] is assumable that nitorgen in almost any form may be utilized by microörganisms, but only certain forms of proteid will yield indol under any circumstances. Many forms of nitrogenous matter reach the ileocecal valve, but only a few contain preformed indol, or are capable of yielding it. These factors would certainly affect the indican output, to what extent it is most difficult to estimate, except that the evidence seems to favor the view that as an end-product there would be a minimum production of indol.

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[4] St. Petersb. med. Woch., 1894, Nr. 28.

[5] Vide article by Fr. Müller in v. Leyden's Handbuch der Ernähungstherap., 1903, i, 162.

[6] Journ. Anat. and Physiol., 1890–91, xxv, 421. These figures must be taken with a great deal of latitude, as the conditions are probably varying. There is no more certain way of causing increase in indican excretion than by excessive ingestion of proteid food. On the other hand, this does not cause a *proportionale* increase in fecal nitrogen. The difference probably falls prey to bacterial activity as soon as the assimilation limit is reached.

[7] With regard to fecal nitrogen, it may be said that if a complete partition could be made in health and disease, it would give us much information as to the intensity of bacterial processes above. This would *not* be a measure of the intoxication. Only that part which is absorbed is concerned in the latter process. For this reason intestinal putrefaction in the maintenance of nitrogen balance is ignored, as the factors tend to balance each other to a small fraction.

Bacterial Considerations. According to the view originally advanced by Bienstock[8] and now generally accepted, Bacillus coli and other facultative aërobes which are "normal" inhabitants of the bowel, are regarded as defensive organisms as opposed to certain obligatory anaërobes (Bacillus aërogenes capsulatus, Bacillus bifidus, etc.), which are regarded as putrefactive organisms and capable of originating pathological putrefactive changes in the intestinal contents. Bacillus coli and its associates exist in a vegetative state, limited in their activities by a peculiar combination of circumstances and by active defences of the host. They expend most of their energy normally in propagation. They cannot attack native proteid, but do form indol. On the other hand, the obligatory anaërobes do disintegrate native proteid at the expense of some time and effort, but they are unable ordinarily to liberate indol (Rettger[9]). Putrefaction of proteid without anaërobes is impossible. Therefore indol formation results from the intervention of Bacillus coli and related forms, acting either on the products of anaërobic activity or on the products of normal proteolytic digestion which have passed along unabsorbed.[10] A good deal of stress is placed on this last point for this reason: ordinary attacks of biliousness in young people, accompanied by large indican excretion and resulting from overeating, presupposes, unless the above alternative be accepted, a complete and sudden change in the bacterial content of the bowel. This seems inconceivable, particularly as the condition yields to proper treatment in a few hours, which in turn presupposes quite as sudden a reversal in bacterial relations to the normal.[11] It is also possible on this hypothesis to account for other discrepancies in the theory of enterogenic intoxication, of which space forbids further consideration.[12]

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[8] Arch. f. Hyg., 1901, xxxix, 390. [9] Jour. Biol. Chem., 1906, ii, 71.

[10] There is some reason for believing that the production of indol as an end-product is dependent on the integrity of the pancreatic secretion, or at least on the ability of the gastro-intestinal secretions, to hydrolyze to the peptone stage.

[11] Vide Herter, Jour. Biol. Chem., 1906, ii, 65, §12.

[12] The products of proteolytic digestion—the carbon nuclei and particularly peptones—are themselves capable of causing intense inflammatory disturbances in the enteron, particularly in concentrated form. This is so well known among laboratory workers that certain types of experimental work cannot be carried on without strictest precautions. There is also a very sharp limit to the capacity of the small intestine to assimilate and rehabilitate carbon nuclei into body proteid. This is especially true if the mucosa is in a state of catarrhal inflammation.

VARIATIONS IN THE ABSORPTIVE POWER OF THE INTESTINE FOR INDOL. It is by no means certain that under strictly normal conditions the mucosa of the large intestine absorbs any considerable quantity of indol, even if elaborated. That it does so in a vast majority of adults is no argument that it is normal in the strictest sense of the term.[13] Some light is thrown on this question by estimating the indol which appears in the feces and comparing it with the amount of indican excreted by the kidneys. Baumstark[14] has made such determinations and found that, with one exception, fecal indol was much greater than urinary indican. This occurred in presumably healthy persons and in those suffering from disease.[15] It would seem as if this variability in absorption is the first defence of the organism against the products of intestinal putrefaction. For this reason, if for no other, any method of diagnosticating the presence of enterogenic intoxication by estimating proteid purefactive products in the feces is fallacious.

What has been said of the absorption of indol applies more particularly to that part of the intestinal tract which lies below the ileocecal valve—to that part in which "normal" putrefaction takes place. In admittedly pathological conditions (such as ileus) putrefaction and the formation of indol is very rapid, and the appearance of indican in the urine is prompt and excessive (Ellinger and Prutz[16]). One can hardly refrain from saying that these very differences in absorption contribute in a striking manner to the value of the indican reaction as indicative of intestinal putrefaction, for in that part of the intestine in which indol is most readily absorbed its presence is certainly pathological.

The detoxication of indol—by union with sulphuric acid and potassium subsequent to oxidation—occurs mainly in the liver. Indoxylpotassium sulphate is, of course, indican. Any combination which the liver may make with glycuronic acid instead of sulphuric acid represents a distinct loss to the urinary reaction for indican. This union is not excessive, and probably happens only when the production of sulphuric acid esters is in great excess and the supply of sulphuric acid ions is limited (Schmiedeberg[17]).

Between the intestinal tract and the urine there is a great loss of indol, totaling to from 40 per cent. to 75 per cent. (Jaffé, Wang, Ellinger[18]). What is the fate of this lost indol? Herter and Wakeman[19] found that the "living cells of the body and especially the hepatic and renal cells and the epitheliated cells of the intestinal tract have the power of absorbing considerable quantities of indol, as well as phenol, and tying them loosely in such a way that these bodies cannot be recovered by distillation." The proper interpretation of this phenomenon may lie in two directions. There is a possibility that a certain portion of indol in an organism with vigorous oxidative capacity is disintegrated into primary carbon and nitrogen groupings, to be recombined in other ways or eliminated as simple end products and thus lost.[20] On the other hand, have we here another manifestation of defensive action on the part of the organism in that the cells at large are able to store indol or its derivatives—withdrawing it from circulation—until such time as circumstances and capacity permit of release in detoxicized form? Perhaps both elements play a part. The point of interest is the loss of indol in transit. It seems quite certain that the organism may change this factor within limits at different times.[21]

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[13] One would hardly argue that because 95 per cent. of those people who come to autopsy after the fiftieth year, show evidence of nephritis, that this is a normal condition.

[14] Münch. med. Woch., 1903, 722. Observations on the relation of fecal indol to urinary indican in healthy children would probably solve this problem.

[15] Baumstark's exception was a girl, aged eleven years, suffering from septic peritonitis. It is of interest to note with this that Herter (Jour. Biol. Chem., 1906, ii, 6) in cases of pernicious anemia, made similar comparisons. He found—judging from the table given—that there was no parallel between the two. In both these conditions the intestinal tract is in an abnormal condition. The inference is plain. Furthermore, indol elaborated in the small intestine would be much less liable to reach the feces owing to the fact that the absorptive power of the small intestine for indol is very great even in health.

[16] Zeit. f. Physiol. Chem., 1903, xxxviii, 399.

[17] Arch. f. exp. Path. u. Pharm., 1881, xiv, 288.

That normal bile contains both ethereal sulphates and glycuronates in traces has been noted by Hammarsten. Whether in pathological states this amount can be materially increased, thus delaying or preventing excretion by the kidney, is not known.

We are uninformed as to the capacity of the kidney for the elimination of indican presented to it by the blood stream. In general, renal epithelium takes kindly to sulphur in any form, for even in renal disease the elimination of sulphur parallels that of nitrogen. Sulphates are excreted in the same ratio as urea, until the rate of elimination reaches a certain excessive point when the kidney refuses to maintain the ratio (Cushney).[22] However, this may not apply to ethereal sulphates. If one may reason from analogy, there may be occasions in the course of a nephritis when, by reason of great excess, portions of indican or its precursors are retained in the blood or there may be variations in the rate of excretion. Possibly the regulating mechanism lies further back and the excess is retained or fixed in the body cells until the serum concentration has sufficiently diminished to permit its release. Brain tissue has this power (Herter).

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[18] Jaffe, Virchow's Archiv, 1877, lxx, 78. Wang, Ziet. f. physiol. Chemie, 1899, 27, 557. Ellinger and Gentzer, Hofmeister's Beiträge, 1904, iv, 171.

[19] Jour. Exp. Med., 1899, iv, 307.

[20] The benzene ring is exceedingly refractory to disintegration, and it is broken up by the organism only at the expense of considerable energy. In considering the toxicity of indol or any of its derivitives, this point must be kept in mind, that excessive quantities of indol thrown into the circulation for a long period of time may impair oxidative capacity. It could hardly be claimed, for instance, that one three-finger glass of whiskey is "toxic." However, a man who made a practice of taking three such drinks a day for ten years will present plenty of evidence of it even if considerable carbohydrate has been spared in the process.

[21] Part of this loss may undoubtedly be accounted for by technical difficulties in the recovery of all the indican excreted.

[22] Jour. of Physiol., 1901-02, xxvii, 429.

Jaffé's original estimate[23] of the "normal" excretion of indican for twenty-four hours was based on observations made on eight presumably healthy people. One excreted no indican at all, and one excreted over 19 mg. The average for the eight was 6.6 mg. It was therefore concluded that the normal output was from 5 to 20 mg. per diem. But the difficulty has been to determine just what the word "normal" should signify. If by it is meant "ideally normal," Jaffé is unquestionably wrong—there should be no indican excretion. I am satisfied of the truth of this for two reasons. The urines of heathy children rarely contain appreciable quantities of indican. The same can usually be said of those adults of middle life whose organisms are in good condition and particularly those whose habits as to the use of meat are moderate. Chittenden[24] found during the course of his dietary experiments that the urinary ethereal sulphates gradually disappeared. Fermentative and putrefactive properties of the feces diminished, as "Fletcherizing" subjects naturally ingested less meat, according to observations made by Fisher.[25]

It seems quite possible that the organism might excrete 20 mg. indican daily and not suffer symptoms thereby, provided the oxidative capacity is high and the process does not extend over too long a time. Either of these provisions violated, and the subject will straightway seek a doctor. On the other hand, less than 20 mg. may suggest the source of subjective symptoms if the oxidative capacity is low. In this class of cases the interpretation of the reaction really resolves itself into an inquiry concerning the ability of the patient to detoxicize products of intestinal putrefaction which may be arising at the time.

But if we assume with Jaffé that 20 mg. is about the limit of normal excretion, there is in this a basis for calculation with Obermeyer's reaction,[26] which may be depended upon for clinical purposes;

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[23] Pflüger's Archiv, 1870, iii, 448.

[24] "Physiological Economy in Nutrition."

[25] Trans. of the Conn. Acad. of Arts and Sci., 1907, xiii, 13.

[26] Until very recently Obermeyer's reagent was used for determining quantitative estimations of indican, but it does not yield constant results. There may be as much as 20 per cent. loss (Ellinger, Zeit. f. physiol. Chemie., 1903, xxxviii, 178). This loss is *liable* to be greater with the Jaffé reaction as applied to qualitative work. There is a great temptation to use too much of the oxidizing agent (potassium permanganate, etc.), which further oxidizes and decolorizes the indigo-blue. The agents should be fresh. When the urine, acid, and oxidizing agent are mixed, they should commingle at the same time, after the manner suggested by Emerson, and not as usually done by mixing two and adding a third. After the mixture is made with either reaction, it should be turned against the finger once and allowed to stand for five minutes. Heating to blood heat before adding the chloroform will also assist. According to Ellinger, there is a loss of 10 per cent. even under the most favorable circumstances. If quantitative estimations are desired, it is well to remember that in urines with high indican content, variations in the quantity of oxidizing reagent and chloroform are necessary to insure maximum color. The better method is to dilute the urine with known quantities of water in the presence of an excess.

20 mg. of indican in 1000 c.c. of urine will yield with Obermeyer's reagent, as ordinarily practised in the laboratory, an index of somewhere between 50 and 75 on Folin's scale.[27] An index of 100 or several times that amount is not uncommon. Heeding all factors given above as necessary for the production of such indices, it must be evident that such a symptom and the intoxication it represents is worthy of very serious consideration, particularly if there is any tendency for it to continue, or if it is accompanied by evidences of digestive, hepatic, or renal disease. Perhaps the following will present some working rules until something better is devised:

1. Urinary indican is a product of intestinal putrefaction. There may be putrefaction without the production of indol, but there cannot be indicanuria without putrefaction.
2. A maximum excretion of indican, that is, an amount which on Folin's scale gives an index of 100 or over, may be safely relied upon to indicate excessive intestinal putrefaction, and especially the intoxication arising therefrom.
3. A maximum reaction which gives an index under 100 may be significant, but its interpretation should be strictly guarded by the general condition of the patient, that is, by the oxidizing and excretory capacity.
4. A heavy indican reaction which markedly subsides under treatment undoubtedly indicates a lessening intoxication, but minor variations in the color index have no significance at present.
5. No interpretation can be placed on a negative reaction, too many unsolved factors entering into the problem.

These are the rules which have been followed in my practice for some time, and which I have found very satisfactory. It is conceded that they are not perfect, but they furnish a practical working hypothesis. It must also be stated that in singling out one of many putrefactive products it has been impossible to do other than take a very narrow view of the subject as a whole. There is much more evidence on the condition of which indicanuria is an indication, but it cannot be presented here. Due allowance must be made for these considerations if the principles herein are to be applied to concrete cases in which intoxication arising from intestinal putrefaction is suspected.

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[27] Otto Folin (Amer. Jour. of Physiol., March, 1905), as a matter of convenience, in reporting some urinary examinations, used a scale based on the color of Fehling's solution. A urine which precipitated a color with Obermeyer's reagent equal to Fehling's solution was said to have an indican index of 100. Exact determinations were obtained by diluting either the urine or the Fehling's solution according to the index, whether above or below 100.